

9. CHARACTERIZATION OF HEALTH HAZARD AND DOSE-RESPONSE FOR DIESEL ENGINE EXHAUST

9.1. INTRODUCTION

Earlier chapters focused on specific health assessment topics and developed key findings for these topics or provided an overview of relevant background information. This chapter will integrate the key findings about health hazards and dose-response analysis for humans exposed to diesel exhaust (DE). Health hazard characterization and dose-response analysis are two of the four components of risk assessment. A third component, exposure assessment, is not within the scope of this report, though an environmental exposure perspective is included in Section 2.4 to assist in evaluating some aspects of the available toxicological information. The fourth component, a population-based risk characterization for environmental exposures to diesel engine exhaust, is beyond the scope of this document.

For introductory purposes, an overview of themes from the key assessment areas will help put the remainder of this chapter into perspective.

- The DE particle and its coating of organics, as well as the accompanying gases and semivolatiles, have biochemical and toxicological properties that raise suspicions about adverse health effects for DE given a sufficient dose, dose-rate, or cumulative exposure.
- Because DE is a mixture, the choice of a dosimeter for measuring exposure is important; $\mu\text{g}/\text{m}^3$ of diesel particulate matter (PM) is used as the dosimeter for the entire DE mixture.
- Ambient exposures to DE vary widely depending on the proximity to sources of diesel engine emissions, including on-road vehicles, off-road machinery, railroad locomotives, and ships. Generally speaking rural locations have lower concentrations of DE than do urban areas, and proximity to occupational settings where diesels are in frequent use provides opportunities for even higher exposures. The margin between high end environmental exposures and occupational exposures is of interest.
- Noncancer toxicity: For chronic exposure, there is scanty human but much animal evidence for adverse respiratory effects, such as airway restriction, inflammation, and related measures of pulmonary histopathology. Acute exposure in humans may elicit symptoms of irritation, ranging from annoying or temporarily debilitating symptoms reflecting tissue irritation. An emerging concern is the possible role of DE in exacerbating or initiating allergenic effects following acute or chronic

exposure. The similarity or difference in these DE effects compared with ambient fine particulate matter is of interest.

- Carcinogenicity: Occupational epidemiologic studies, using surrogates for DE exposure, show a pattern of increased cancer risk for the lung. Most rat and some mouse inhalation studies show a carcinogenic response in the lung at high test exposures; in the rat these responses occur under conditions of particle overload. Organic components of DE have known or suspected mutagenic/genotoxic and carcinogenic properties. Mode-of-action information provides a framework to evaluate the observed lung cancer responses and judge the confidence in establishing the human hazard potential as well as suggesting the best approach for conducting dose-response analysis and estimation of cancer unit risk.

9.2. WHAT IS DIESEL EXHAUST IN A HEALTH HAZARD ASSESSMENT CONTEXT?

DE is a complex mixture of literally hundreds of components. As reviewed in Chapter 2, the mixture consists of particles and gases. The particulate matter consists of an elemental carbon core particle with hundreds of organic and some inorganic compounds adsorbed to the particle surface. The gaseous fraction is also made up of many organic and multiple inorganic compounds. Some organics and inorganics also exist in a semivolatile state. The elemental carbon core, the particle coating of adsorbed compounds, and the gaseous and semivolatile elements each have constituents with known toxicological properties, and in addition there is a possible aggregate toxicological potential for the whole mixture.

The DE particle fraction is made up of a distribution of particle sizes (e.g., nano/ultrafine particles of 0.005-0.05 μm mean mass aerodynamic diameter), as well as clusters of aggregated particles (e.g., fine particles of 0.05-0.7 μm MMAD) and a small number of larger particles (e.g., coarse size of 1.0-10.0 μm MMAD) (Section 2.6.5). Typically the particles average about 0.2 μm MMAD and have a very large surface area (50-200 m^2/g). Most of the particle mass is in the fine size range, while the majority of the particles are in the nano/ultrafine range. The vast majority of DE particles will be present in a $\text{PM}_{2.5}$ fraction of total PM. In any given ambient PM sample, diesel particles may or may not be present, depending on the proximity to a diesel emission source. The diesel particle is crudely distinguishable from other PM by virtue of its elemental carbon core and possibly certain qualitative or quantitative differences in the adsorbed organics. DE may contribute significantly to total ambient PM: for instance, Schauer et al. (1996) reported nationwide diesel contributions to total $\text{PM}_{2.5}$ mass of 12.8%-35.7% in several urban California regions in 1982, whereas the more current Denver area NFRAQS (1998) study showed diesel $\text{PM}_{2.5}$ to be 9.7%-10.2% of total $\text{PM}_{2.5}$ mass. The U.S. EPA Air Quality Planning and Standards

1 report on air pollutant trends indicates that annual emissions of diesel PM_{2.5} nationwide are 5.7%
2 of the total PM_{2.5} inventory and 21% of the inventory excluding natural and fugitive dust sources.

3 The diesel particle size distribution is significant for exposure-response purposes because
4 smaller particles have a greater likelihood of being deposited more deeply in the lung than do
5 larger diameter particles. Additionally, smaller particles have a larger surface area per unit of mass
6 and therefore may adsorb and transport more organic compounds into the respiratory system than
7 the same mass of larger particles, and may elicit more of an inflammatory response characteristic of
8 poorly soluble particles (Section 7.4.1). From these circumstances, it would be suspected that DE
9 particles may have a different (e.g., increased) potential for toxicological consequences compared
10 to larger particles of other than DE origin.

11 The main constituent by weight of the diesel particle is elemental carbon (Section
12 2.2.6.1). Various studies show the DE particle composition to vary considerably, with the
13 elemental carbon content ranging from 30% to 90% of total mass, with 80% being typical. (For
14 reference, PM from gasoline engine exhaust typically has a much smaller fraction of elemental
15 carbon and a large organic fraction.) The DE inorganics include nitrates, compounds of sulfur,
16 and some carbon monoxide. The DE particle organics include many compounds, a number of
17 which are considered to have a mutagenic and carcinogenic hazard potential for humans (see Table
18 2-9 for classes of compounds), though the concentrations of the organics are generally low. Many
19 PAHs and PAH derivatives are toxic, especially the nitro-PAHs. Many of the compounds emitted
20 as gases are also potentially carcinogenic or otherwise toxic at some dose, though not necessarily
21 known to be toxic to the lung. These include benzene, 1,3-butadiene, various aldehydes, ethylene
22 dibromide, nitroaromatics, oxides of nitrogen, and sulfur compounds. Additionally, there is
23 evidence that the mixture of organics emitted and as altered in atmospheric transformation
24 provides the chemical species necessary for the formation of free radicals (e.g., reactive oxygen or
25 hydroxyl species formed from certain organics with or without mammalian metabolism); free
26 radicals are known to cause DNA damage in biological systems (Section 7.4.3). The
27 quantitative physical-chemical composition of any discrete diesel exhaust depends on numerous
28 factors, including operating conditions, heavy-duty versus light-duty engines, engine design, engine
29 age, fuel used, exhaust control technology, and the sampling and measurement system used.
30 Diesel particle measurement in the laboratory under controlled conditions versus sampling in the
31 ambient environment is likely to produce varied results, because the formation of particles is
32 influenced by dilution ratios and conditions of temperature and humidity. These factors mostly
33 affect particle size but may also affect particle composition. The available human and animal
34 studies were based on engine exhaust representative of engines and conditions at various times
35 since 1980, while some of the epidemiology studies cover exposures from the 1950s through the
36 mid 1980s. This leads to two questions: how the physical-chemical nature of the past exposures

1 compares to present-day exposures, and how applicable the toxicological results generated from
2 the older exposures are to current-day DE exposure-related hazards. These questions frame a risk
3 assessment uncertainty for which there are no definitive answers.

4 The overwhelming majority of the emission, exposure, and toxicological data uses particle
5 emission mass expressed in units of $\mu\text{g}/\text{m}^3$ for DE measurement. This was assumed early on by
6 researchers to be a useful dosimeter. At first glance this approach seems to ignore the gaseous
7 component and it does not distinguish between elemental carbon and the accompanying organics.

8 In Sections 2.2.6 and 2.2.7 an attempt is made to characterize the changes in engine
9 emissions over the years, taking into consideration the lack of consistent and reliable data and the
10 variability of in-use engines. What can be crudely inferred from the available data is that trends in
11 the emission composition over the years have not changed much, qualitatively, though some
12 quantitative changes are discernible in the past 20 years. By analysis, on-road diesel engine
13 particulate emissions were reduced about sixfold, at most 10-fold, on a g/mile basis from 1977 to
14 1997. Both the elemental carbon and organic content are decreasing. The decrease in organics is
15 mostly a consequence of engine designs that seek to reduce oil consumption. Available research
16 suggests that while most PAH emissions, including nitro-PAHs show a declining trend on a g/mi
17 basis, the overall PAH composition profile has not changed significantly. There is no available
18 evidence that toxicologically significant organic components of DE (e.g., PAHs, PAH derivatives,
19 and nitro-PAHs) have significantly increased or decreased out of proportion to the change in
20 organic mass. Limited particle size measurements suggest that current engine emissions may have
21 higher concentrations of nano/ultrafine particles; however, the methods for measuring these
22 particles are in an early stage of development, and at the moment there is little concrete evidence
23 that modern engines produce greater amounts of $<0.05\ \mu\text{m}$ particles than older engines. Given this
24 information and recognizing the extensive use of $\mu\text{g}/\text{m}^3$ in published research results, $\mu\text{g}/\text{m}^3$ is used
25 as the dosimeter in this assessment. The best choice of dosimeter and subsequent reduction of
26 uncertainty will only be discernible when there is a better understanding of diesel's toxicological
27 mode of action.

28 The second question, the applicability of past exposure-toxicological results to present-
29 day exposure scenarios, is not fully answerable and thus remains an area of uncertainty. The
30 observation that there is no particular evidence for a major qualitative change in organic
31 composition, especially for PAHs, and that organics can be viewed as proportional to the particle
32 mass provides a rationale for the applicability of prior-year assessment findings to more current
33 exposures when $\mu\text{g}/\text{m}^3$ is used as the dosimeter.

34 Once diesel emissions are released in the air, they are subject to dispersal, dilution, and
35 chemical and physical transformations (Section 2.3.3). Newly emitted exhaust is termed "fresh"
36 while exhaust more than 1 or 2 days old is referred to as "aged" because of alterations caused by

1 sunlight and other chemical physical conditions of the ambient atmosphere. It is not clear what the
2 overall toxicological consequence of exhaust aging is, because some compounds are altered to
3 more toxic forms while others are made less toxic. For example, PAHs present in fresh emissions
4 may be nitrated by atmospheric NO₃ to form nitro-PAHs, thus adding to the existing burden of
5 nitro-PAHs present in fresh exhaust; alkanes and alkenes may be converted to aldehydes, and
6 oxides of nitrogen to nitric acid. The atmospheric lifetime for some of the transformed compounds
7 ranges from hours to days (Chapter 2, Table 2-9). On the other hand, PAHs present in the gas
8 phase react with hydroxyl radicals present in the ambient air, leading to reduced atmospheric
9 halftimes of the original PAHs. In general, secondary pollutants formed in an aged aerosol mass
10 are more oxidized, and therefore have increased polarity and water solubility. Comprehensive
11 assessment of the health hazards posed by DE would also consider the hazards posed by the
12 atmospheric reaction products, a task that is not directly addressed in this assessment. In terms of
13 environmental and occupational concentrations of DE, most people exposed to DE receive a
14 mixture of both fresh and aged exhaust, with the proportion of fresh exhaust likely related to their
15 proximity to the source of emissions. On the other hand, the DE used in animal bioassays had a
16 high percentage of fresh exhaust.

18 **9.3. NONOCCUPATIONAL AND OCCUPATIONAL EXPOSURE**

19 While a rigorous and comprehensive exposure analysis for DE has not been conducted as
20 part of this assessment, some exposure information from EPA's Office of Mobile Sources has been
21 included in Section 2.4.3 to provide a context for the hazard assessment and dose-response
22 analysis. Nonoccupational exposure to DE occurs worldwide in urban areas, with lesser exposure
23 in rural areas. The concentration of DE constituents in the air will vary within any geographic area
24 based on the number and types of diesel engines (on-road and off-road) in the area, the
25 atmospheric patterns of dispersal, and the proximity of the exposed individual to the diesel
26 emission source. Certain occupational populations can be exposed to much higher levels of DE
27 compared with a majority of the population.

28 In developing a perspective on human exposure one has to distinguish between airborne
29 concentrations present at any given time versus actual human exposure. Estimates of annually
30 averaged DEP (diesel exhaust particulates) at fixed sites in urban and suburban areas in the 1980s
31 ranged from approximately 4.4 µg/m³ to 11.6 µg/m³ from chemical mass balance (CMB) modeling
32 which covers all (on-road and off-road) sources of emission (Section 2.2.4). Modeling shows that
33 an above-average day, representing a high concentration day, may be in the 10 to 22 µg/m³ range,
34 and that "hotspots" (near highways, bus depots, or other transportation facilities) may range up to
35 47 µg/m³. In a broader sense, DEP concentrations assessed by CMB for both on-road and off-
36 road at fixed sites in suburban and urban areas range from approximately 1.2 to 3.6 µg/m³.

For exposure estimation EPA relies on a Hazardous Air Pollutant Exposure Model which deals with on-road sources only (Section 2.4.4). This model indicates that on an annual basis, the urban population is exposed to levels of DEP from 0.6 to 1.7 $\mu\text{g}/\text{m}^3$. For more highly exposed individuals in urban areas the range is 0.9 to 4.1 $\mu\text{g}/\text{m}^3$. These estimates include projections into the 1990s. Those in the population that have outdoor time in proximity to diesel exhaust sources such as highway truck routes are likely to have a higher exposure during the outdoor time, and thus their annual average exposure is somewhat higher than those with lesser outdoor time.

Recent studies, including a study of the Baltimore Harbor Tunnel (conducted by the Desert Research Laboratory for the American Petroleum Institute) and an ORD measurement study of tailpipe emissions from a moving heavy-duty diesel truck, have confirmed that dioxins are formed and emitted from heavy-duty diesel trucks (Section 2.2.6.4). ORD's dioxin source emission inventory estimates that 60 g TEQ were emitted from heavy-duty U.S. trucks in 1995. This does not account for other vehicular diesel emissions (e.g., diesel automobiles and other truck categories) or any off-road emissions from the many diesel-powered engines. When the heavy duty truck estimate is compared with total estimated U.S. emissions of 3000 g TEQ for 1995, it appears that the heavy-duty diesel trucks are not a major dioxin source. The human dioxin exposures of concern have been primarily noninhalation exposures associated with human ingestion of certain foods, e.g., beef, vegetables, and dairy products contaminated by dioxin. It is unknown whether heavy-duty truck DE deposition has a local food chain impact.

9.4. HAZARD CHARACTERIZATION

9.4.1. Health Effects Other Than Cancer: Acute Exposures

As reviewed in Chapter 5, the most readily identified acute (e.g., usually single-exposure) noncancer health effect of DE on humans is its ability to elicit complaints of eye, throat, and bronchial irritation as well as physiological symptoms such as headache, lightheadedness, nausea, vomiting, and numbness or tingling of the extremities. Such symptoms have been reported by individuals exposed to DE on busy city streets or in bus stations, most of which are case reports without an understanding about the possibility of confounding exposures. Recent human and animal studies also suggest that acute DE exposure episodes may play a role in the development of immunological allergic reactions, possibly resulting in prolonged hypersensitivity to DE and perhaps other ambient contaminants. It is premature to further characterize DE's allergenicity effects until additional information is available.

9.4.2. Effects Other Than Cancer: Chronic Exposure

Based on limited evidence in human occupational studies, but combined with multiple controlled laboratory animal studies in several species, a high level of confidence exists that

1 chronic exposure to DE constitutes a noncancer respiratory hazard for humans. As DE exposure
2 levels and duration increase, the onset of respiratory symptoms in humans is observable, with
3 limited evidence of long-term consequences, whereas in animal studies the onset of symptoms and
4 adverse consequences is more clear and replicable. Current data also identify possible neurological
5 and behavioral effects, though these occur at higher exposure levels than the respiratory effects.
6 Animal studies show a possible high-exposure reproductive effect, but no other reproductive or
7 developmental consequence is identified. Section 5.6 summaries discuss this topic in more depth.

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9 A few human studies in various diesel occupational settings suggest that diesel exposure
10 may impair pulmonary function, as evidenced by increases in respiratory symptoms and some
11 reductions in baseline pulmonary function consistent with restrictive airway disease. Other studies
12 found no particular effects. The methodologic limitations in these studies limit their usefulness in
13 drawing any firmer conclusions (Sections 5.6.1, 5.6.9).

14 There is a considerable body of animal evidence that clearly correlates DE exposure with
15 pulmonary injury. Short-term animal exposures of high concentrations of diesel PM resulted in
16 histological and cytological changes in the lungs, but only minimal effects on pulmonary function.
17 A number of long-term laboratory studies with rats, mice, Chinese hamsters, Syrian golden
18 hamsters, cats, and Cynomolgus monkeys found varying degrees of adverse lung pathology.
19 Histological studies show a variety of changes in respiratory tract tissue, including focal thickening
20 of the alveolar walls, replacement of Type I alveolar cells by type II cells, and fibrosis. Exposures
21 for several months or longer to levels markedly above environmental ambient concentrations
22 resulted in accumulation of particles in the animal lungs and an impaired ability to clear particulate
23 matter from the lungs. While the applicability of rat lung cancer responses to possible human
24 hazard has been questioned, the noncancer rodent responses are thought to be relevant for humans,
25 though the rat is more sensitive than other rodent species and is also suspected to be more
26 sensitive than humans for a number of toxic effects (ILSI, 1998). Because these effects were seen
27 in a wide range of animal species, there is a qualitative basis to believe that humans could also
28 experience hazard for these effects and may be at risk under some condition of exposure.

29 Available data limit current efforts to develop hypotheses regarding specific mechanisms
30 or mode of action for DE's respiratory disease impact on humans. The MoA information comes
31 almost entirely from observing rodents, which demonstrate the following: (1) the particle fraction
32 of DE is involved in the etiology of toxicity, though a constituent role for the particle organics and
33 the DE gases cannot be dismissed; (2) similar particle-driven effects occur in different animal
34 species, although the observable onset varies by species; (3) lung injury appears to be mediated by
35 a progressive impairment of normal lung function by invading alveolar macrophages; and (4) it is

believed that the adverse effects have a biological threshold, there being no available evidence to the contrary.

Animal studies have also suggested that liver and kidney changes may be occurring at high concentrations, along with some indication of neurotoxic effects and impacts on spermatogenesis. Impaired growth rates have also been observed in animals chronically exposed to DE. However, these effects are seen at exposures higher than the respiratory effects. An assessment focused on determining levels that are likely to be protective for respiratory hazards will be protective for all effects observed to date.

Respirable particles in general have been implicated as etiologic factors in various types of chronic human lung diseases (U.S. EPA, 1996). Ambient PM is associated with increased morbidity and mortality, aggravation of respiratory and cardiovascular disease, changes in lung function and increased respiratory symptoms, changes to lung tissues and structure, and altered respiratory defense mechanisms. The majority of DE particle mass is in the low end of the “fine” particle range, and thus contributes to ambient levels of PM_{2.5}.

9.4.3. Health Effects Other Than Cancer: Derivation of Inhalation Reference Concentration

A considerable body of evidence provides a basis to infer a noncancer respiratory health hazard following inhalation of DE. On the basis of pulmonary function and histopathological and histochemical effects in rats, a rough estimate can be made concerning what chronic dose/exposure rates of DE (measured in terms of the concentration of diesel PM) cause an adverse effect and which exposures do not; this then is a starting point for estimating protective margins for human exposure. The available human studies, while qualitatively suggestive of possible adverse effects, were inadequate for RfC determination. A reliable experimental database and established EPA dose-response evaluation methods have been used to derive an inhalation reference concentration (RfC) for chronic exposure to DE.

The derivation of an RfC for DE is a dose-response approach used by EPA for chronic noncarcinogenic effects. An RfC is defined as an estimate of a continuous inhalation exposure to the human population, including sensitive subgroups, with uncertainty spanning perhaps an order of magnitude, that is likely to be without appreciable risks of deleterious noncancer effects during a lifetime. The RfC approach is based on the assumption that a threshold exists for the human population below which no effect will occur. The approach identifies a “critical” effect and related NOAEL; “critical” is defined as the first effect, or its known precursor, that occurs as the dose rate increases. There may be various uncertainties associated with this selection. Second, depending on the critical study, any of several types of uncertainty factors are used to reduce the NOAEL to a level that is thought to be without appreciable hazard to humans. The selection of

1 uncertainty factors is driven by both science and policy considerations focused on uncertainties in
2 the available data or, in some cases, reflecting the absence of data. The resulting RfC is not a
3 bright line (i.e., just above which hazard can be expected); rather, as the human exposure increases
4 beyond the RfC, the margin of protection decreases and the likelihood of hazard is considered to
5 increase.

6 The DE RfC evaluation closely examined 10 long-term (greater than 1 year) DE
7 inhalation studies in laboratory rats. This is beneficial to the process of RfC determination because
8 the data base on the critical effect has an unusually large number of relevant studies (Chapter 6).
9 The available human studies, as discussed earlier, were qualitatively suggestive of adverse effects
10 but were inadequate for RfC determination. Two key rat studies (Mauderly, 1988; Ishinishi, 1988)
11 were selected because each identified respiratory effects after chronic exposure and provided good
12 information about pulmonary histopathology. The selected studies also spanned a wide range of
13 exposures from 350 to 7000 $\mu\text{g}/\text{m}^3$, with three exposures in the 350-960 $\mu\text{g}/\text{m}^3$ range. Human
14 equivalent concentrations (HEC) were calculated from the animal exposure information using a
15 dosimetry model developed by Yu et al. (1991) that accounted for species differences in
16 respiratory exchange rates, particle deposition efficiency, differences in particle clearance rates at
17 high and low doses, and transport of particles to lymph nodes. The adopted RfC evolved from a
18 NOAEL of 460 $\mu\text{g}/\text{m}^3$ (HEC = 155 $\mu\text{g}/\text{m}^3$) that was related to a LOAEL of 960 $\mu\text{g}/\text{m}^3$ (HEC =
19 300 $\mu\text{g}/\text{m}^3$) (Table 6-2). Although particle overload conditions are thought to occur above 1000
20 $\mu\text{g}/\text{m}^3$, the likelihood of lung overload conditions is thought to be minimal at 460 $\mu\text{g}/\text{m}^3$.

21 Two principal areas of uncertainty are present in the RfC derivation (Section 6.1.3). As
22 the RfC is based on a chronic animal study, an uncertainty factor of 10 is usually applied for the
23 animal-to-human extrapolation of an effect to account for the possibility that humans may be a
24 more sensitive species than the rodent. This uncertainty is equally parceled ($10^{0.5}$ each) between a
25 pharmacokinetic (PK) component and a pharmacodynamic (PD) component. As a PK model was
26 used in this assessment to derive the HEC, the uncertainty about the PK component was
27 considered resolved. Application of uncertainty for the PD component was more complex.
28 Although the rat appeared to be clearly more sensitive than humans for the inflammatory responses
29 underlying the observed pulmonary pathology, it was not clear if rats were also more sensitive than
30 humans to those inflammatory processes underlying the observed enhanced allergenicity. In light
31 of this uncertainty, the uncertainty for the PD component is maintained at $10^{0.5}$, which is rounded
32 to 3. A second uncertainty factor of 10 is generally used to account for possible inter-individual
33 variability in sensitivity unless mechanistic or other data suggest otherwise. This uncertainty factor
34 is considered appropriate for the current assessment. The total uncertainty factor is $3 \times 10 = 30$.
35 With 155 $\mu\text{g}/\text{m}^3$ divided by 30, the resulting RfC is
36

$RfC = 5 \mu\text{g}/\text{m}^3$ of diesel particulate matter (DEP).

A comparison of the DE RfC and the PM_{2.5} regulatory standard is not a straightforward endeavor, and caution should be exercised in comparing the output of a health hazard assessment RfC and the product of a science-based regulatory process. Nonetheless, conclusions reached in each of these processes are remarkably similar. EPA's 1997 PM_{2.5} standard is 15 µg/m³, as a 3-year average, based on human studies. The noncancer respiratory effects from DE are qualitatively similar to some of those for PM_{2.5}. The DE particulates can be a component of ambient PM_{2.5}. Compared to ambient PM_{2.5} with no DE component, DE is likely to have a higher proportion of fine and ultrafine particulates and is likely to have a higher or at least a varied content of toxicologically active organic compounds. Although some similarities exist between DE and ambient PM, the differences are potentially significant. A comparison of the DE RfC and the PM_{2.5} standard has considerable complexity.

9.5. CARCINOGENICITY HAZARD CHARACTERIZATION

For inhalation exposure, both human studies and animal bioassays are available for assessment of DE. In fact, both the human and certain aspects of the animal data provide evidence that exposure to DE has the potential to be carcinogenic to humans under some conditions of exposure. Chapter 7 reviews the cancer data in detail. A finding about the hazard potential does not specify the magnitude of the possible impact on an exposed population; this is an issue for dose-response assessment, which is discussed in Chapter 8.

9.5.1. Cancer Hazard

Diesel engine exhaust is "highly likely" to be carcinogenic by the inhalation route of exposure, according to EPA's 1996 Proposed Guidelines for Carcinogen Risk Assessment. This hazard is viewed as being applicable to ambient (i.e., environmental) exposures. There is no available evidence to evaluate the hazard from other routes of exposure. The "likely" characterization generally compares with the weight-of-evidence designation "B-1, probable human carcinogen" from the EPA's 1986 Guidelines for Carcinogen Risk Assessment. The overall weight of evidence for DE places it at the upper end of the grouping and hence gives the "highly likely" designation (Section 7.5). The carcinogenic potential of DE is indicated by: (1) consistent association between observed increased lung cancer and DE exposure in certain occupationally exposed workers; (2) induction of lung cancer by whole DE and DE particles in some, but not all, inhalation animal bioassays; (3) induction of cancer from various fractions of the DE mixture, as shown in skin painting, intratracheal, and other noninhalation animal test systems; and (4) the presence of organics on the diesel particles and in the DE gases, some of which have potent

1 mutagenic and carcinogenic properties in their own right, as well as some evidence for the
2 bioavailability of the organics. The mode of action for carcinogenicity in humans is unknown,
3 though it could be suggested that either or both the organics in the DE and the elemental carbon
4 diesel particle contribute to the carcinogenic activity.

5 Increases in relative risk for lung cancer have been consistently noted in a number of
6 epidemiologic studies, and causality considerations for this observed association are very
7 consistent with DE exposure being causally related to lung cancer (Section 7.5.1) Aggregate
8 estimates from meta-analysis of the statistically increased relative risks for smoking-adjusted
9 studies are 1.33 in one analysis and 1.47 in another (33% or 47% increase in lung cancer above
10 background), though individual studies, such as Steenland et al. (1990), had higher relative risks
11 (e.g., 1.64 and 1.89) for specific groups of workers. Meta-analyses are a tool to evaluate relative
12 risk estimates from multiple compatible studies. Although the approach weights the influence of
13 individual study results in the overall outcome, the analysis does not override uncertainties or
14 limitations in the individual studies. A very recent publication provides yet another pooling of
15 diesel occupational exposure-lung cancer data from two large case-control studies in Germany
16 (Brüske-Holfeld et al., 1999). The aggregate relative risk results were similar to those previously
17 mentioned, with some specific job categories having relative risks greater than 2. This paper will
18 be evaluated further before this assessment is finalized.

19 The uncertainties with the DE epidemiology data are the typical ones including the
20 possibility that chance, bias or confounding are influencing the observed lung cancer increases
21 (Section 7.2.6.5). The persistence of the lung cancer association in multiple studies and statistical
22 confidence limits in key studies indicates that chance alone is unlikely to account for the observed
23 relation between DE and lung cancer. A causal interpretation for DE is enhanced when the “Hill”
24 causality criteria are evaluated, noting that an absence or weakness in one or several of the criteria
25 does not prevent a causal finding, though it could be a basis to limit one (Section 7.2.6.6). A
26 weakness in the epidemiology studies showing a positive association is that diesel exposure is
27 inferred from job codes, area descriptions, and the like, which are surrogates for the true
28 underlying exposure. This can lead to nondifferential misclassification of exposure, and while
29 unlikely this might result in a spurious risk estimate in any one study. It is even more unlikely,
30 however, that it would bias a sufficient number of studies in a uniform direction to account for the
31 persistent association observed. Moreover, any bias would likely be toward a lower risk estimate.
32 Not all studies controlled for a tobacco smoke effect. In those studies that did adjust for smoking,
33 there remains a possibility that the adjustment may not be completely effective, and residual
34 confounding by smoking may persist to bias the correlation of DE exposure with lung cancer
35 occurrence. This uncertainty is currently unresolvable.

1 An inability to satisfactorily minimize all confounding, bias, and exposure uncertainties has
2 resulted in the human evidence being judged not quite adequate to support a finding of causality
3 and characterization of DE as a “known” human carcinogen. Others looking at the same evidence
4 may reach slightly different conclusions as scientific judgment is involved. Cal-EPA, for instance,
5 has judged the epidemiologic evidence to be sufficient to support a causality finding under its
6 criteria. Others, HEI (1995) for example, have argued that human data are consistent in showing
7 weak associations between DE exposure and lung cancer, but that there is insufficient evidence to
8 conclude whether confounding and exposure uncertainties have influenced the association.

9 While lung cancer has been induced experimentally in rats via inhalation of DE at high
10 exposure concentrations, the data show that the primary factors that are likely to be responsible for
11 lung cancer are high particle concentrations producing a particle overload in the lung, and
12 subsequent induction of persistent inflammatory responses, followed by DNA damage, rapid cell
13 turnover, and eventual lung cancer (Section 7.4.2). This mode of action for lung carcinogenicity in
14 the rat under overload conditions is thought to be unique. It is not known whether humans have a
15 similar response pattern at high exposures, although such a pattern has not been historically
16 observed. Overload inflammatory responses are not seen at rat test exposures below $1000 \mu\text{g}/\text{m}^3$
17 (estimated HEC $300\text{--}350 \mu\text{g}/\text{m}^3$), but lung impacts still occur under the nonoverload condition.
18 Uncertainty remains as to whether induction of inflammatory responses or other forms of lung
19 injury in humans will lead to lung cancer. Therefore, there are insufficient data to conclude that
20 the rat response is completely irrelevant for a human hazard characterization. The high-exposure-
21 related rat lung cancer responses, however, are unsuitable for estimating risk at lower
22 environmental levels of exposure in humans.

23 Generally, rats showed significant increases in lung tumors beginning at exposures of
24 $>2200 \mu\text{g}/\text{m}^3$ (HEC is approximately $700\text{--}900 \mu\text{g}/\text{m}^3$). These exposure levels clearly represent lung
25 overload conditions for the rat. In addition, these human equivalent exposure concentrations are
26 significantly higher than those found in the human occupational studies discussed in Chapter 7.
27 These range from about $3 \mu\text{g}/\text{m}^3$ as an environmental equivalent calculated from the Teamster’s
28 Union truck study (Steenland et al., 1998, Section 8.3.8.2) to $141\text{--}192 \mu\text{g}/\text{m}^3$ (and possibly up to
29 $500 \mu\text{g}/\text{m}^3$), which is reported as an occupational level in the railroad worker study (Woskie et al.,
30 1988b and others). These reported levels overlap with, but range significantly higher than,
31 nationwide ambient continuous exposure estimates for humans of $0.6\text{--}4.1 \mu\text{g}/\text{m}^3$, not counting
32 hotspots (Section 2.4.3).

33 Organic extracts of DE particles have been shown to induce tumors in mice, both by skin
34 painting, and subcutaneous injection, and to be mutagenic in several test systems. Additionally, a
35 number of PAHs and nitro-PAHs present on diesel particles as well as in the vapor phase are
36 known to be mutagenic and/or carcinogenic. As discussed in Section 7.3.2, filtered DE (i.e.,

exposure to DE gases) does not produce a lung tumor response in rats. Intratracheal studies (Section 7.3.4) show that DE particles with and without organics elicit a lung cancer response, as does a pure elemental carbon particle, carbon black, with a modestly higher response for the whole DE particle. Also, four- to seven-ring PAHs are shown to be a particularly potent fraction of the organic extracts.

The plausibility of an environmental lung cancer hazard from DE by inhalation exposure is supported by findings contained in this assessment: (1) that mutagenic and tumor initiating carcinogens are present in small quantities in the DE organic mixture; (2) that some bioavailability of the organics is expected and that deposited particulates seem to have much longer residence times in humans than in animal species. This provides an extended opportunity for elution, metabolism if needed, and uptake of the organics. These organics include many well characterized mutagens and carcinogens; and (3) that there may be a relatively small margin of exposure between higher end environmental exposures and some occupational levels in studies where statistically increased aggregate relative risks in the range of 1.33 to 1.47 are seen (e.g., exposure estimates for some truck drivers could be overlapping some environmental estimates).

Overall, the evidence for a likely human lung cancer hazard by inhalation is persuasive, even though, in the absence of complete data, inferences and thus uncertainties are involved. Some of the key uncertainties include: (1) methodologic limitations inherent in epidemiologic studies, as well as a lack of reliable historical exposure data for occupationally exposed cohorts, (2) uncertainties regarding the extent of bioavailability of organic compounds present on diesel particles and their impact on the carcinogenic process, and (3) other uncertainties regarding the mode of action of DE on lung cancer in humans.

The epidemiologic evidence for DE being associated with other forms of cancer is inconclusive.

9.6. CANCER DOSE-RESPONSE ASSESSMENT

Cancer dose-response assessment describes what is known about the relationship of exposure/dose to a cancer response (e.g., lung cancer) and how the response might change with dose within the range of empirical observations. It also evaluates the applicability of this relationship to human low-exposure circumstances. The low-exposure aspects are approached by extrapolation, if appropriate, from an observable response range to lower exposure/dose levels, such as ambient levels of interest. Key choices in dose-response assessment are influenced by epidemiologic and toxicologic data and informed by reasoning about the possible mode(s) of action. In the absence of such information, standard assumptions (i.e., defaults) are used, many of which are conservative toward public health protection. Chapter 8 contains a more detailed review of dose-response issues.

Human data are preferred as a starting point for DE dose-response assessment, one purpose of which would be to estimate cancer potency (i.e., cancer unit risk). Unit risk is the estimated cancer risk at 1 $\mu\text{g}/\text{m}^3$ of exposure for a lifetime; in this case, $\mu\text{g}/\text{m}^3$ of DE particulate matter from a continuous 70-year exposure. Unit risk derivation procedures and specifications are defined in EPA's risk assessment guidance.

The overall challenge with DE is to judge the uncertainties in the dose-response analysis, given available data, and to decide whether to proceed. If the analysis is carried out, it is important to decide what certainties/uncertainties to ascribe to any resulting output of the analysis and follow-on unit risk derivation.

The mode of action (MoA) for humans is unknown, and the presumed MoA for rats does not justify using rat lung tumor data to estimate low-exposure cancer risk for humans. This report concludes that a role for organic-mutagenic/genotoxic constituents of DE as well as a role for particles is plausible, recognizing that the relative contributions of each may vary with dose-exposure. With organics thought to be in relative proportion to the mass of particulates, the use of $\mu\text{g}/\text{m}^3$ of DE particles as the dosimeter is feasible. With no clear indication that key organic components have changed disproportionately to total organics over the years (Section 2.5), the use of toxicological results based on older engine exposures to predict current-day hazards is also feasible, though uncertainty exists.

Section 8.2 reviews a number of past attempts to estimate diesel cancer potency (i.e., unit cancer risk) using epidemiology data, rat data, and comparative potency approaches. With the rat estimates now being thought unsuitable, the comparative potency-based estimates having limitations and thus being uncertain, and the epidemiology-based estimates having outstanding issues and questions to be resolved, these historical risk estimates lack a consensus of support. With ongoing investigations to update mortality in the Garshick railroad worker study and additional review and analysis of the Steenland et al. (1998) study underway, the Agency has determined that there is no scientific support for further analysis of the existing epidemiologic data until some newer information is available. Additional information is expected over the next few years.

A decision has been made in this assessment that, despite the finding that DE is best characterized as highly likely to be a lung cancer hazard, the available data are currently unsuitable to make a confident quantitative statement about the magnitude of the lung cancer risk attributable to DE at ambient exposure levels. Therefore, this assessment does not adopt or recommend a specific cancer unit risk estimate for DE. However, information is provided in Section 8.3 to put DE cancer hazard in perspective and to assist decisionmakers and the public to make prudent public health judgments in the absence of a definitive estimate of the upper bound on cancer risk. This perspective is based on the consistent observations of a relatively low (~40%) increase in

relative risk and the power of epidemiologic studies to detect low levels of absolute risk. In addition, Section 8.2 describes the use of historic approaches that consider comparative potency to inform the perspective. This discussion leads to the conclusion that the available science can support a position that, if one accepts the conclusion that DE has human carcinogenic potential, risks may be in the range of regulatory interest ($>10^{-6}$ or 1 in 1 million), but that they are not likely to exceed levels that often result in immediate regulatory action ($>10^{-3}$ or 1 in 1000). The Agency does not believe that the current data support a more precise perspective.

9.7. SUSCEPTIBLE SUBGROUPS

The hazards previously characterized, i.e., acute and chronic effects, are assumed to be possible consequences in individuals of average health and in their adult years. There is no DE-specific information that provides direct insight to the question of variable susceptibility within the population. Default approaches to account for uncertainty in inter-individual susceptibility have been included in the derivation of the RfC. Individuals with preexisting lung burdens of particulates may have less of a margin of safety from DE particulate-driven hazards than might be inferred from incremental DE exposure analysis, although this cannot be quantified. DE exposure could be additive to many other daily or lifetime exposures to organics and PM. For example, adults who predispose their lungs to increased particle retention (e.g., smoking or high particulate burdens from nondiesel sources), have existing respiratory or lung inflammation or repeated respiratory infections, or have chronic bronchitis, asthma, or fibrosis could be more susceptible to adverse impacts from DE exposure. Although there is no information from studies of DE, infants and children could have a greater susceptibility to the acute/chronic toxicity of DE because they have greater ventilatory frequency, resulting in greater respiratory tract particle deposition (U.S. EPA, 1996b). The issue of DE impacts on allergenicity and potential onset and exacerbation of childhood asthma is being actively investigated, but firm conclusions await peer review and publication of ongoing work.

Another aspect of differential susceptibility involves subgroups that may receive additional exposure to DE because of their proximity to DE sources. Earlier it was mentioned that those having outside time in their daily routine and being near a diesel emission source would likely receive more exposure than others in the population. The highest exposed are most likely the occupational subgroups whose job brings them very close to diesel emission sources (e.g., trucking industry, machinery operations, engine mechanics, some types of transit operations, railroads, etc.).

9.8. REFERENCES

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